

Box 1 Explicitly prohibited foodstuffs

Chewing gum, candy, and similar products

Spices and herbs (except salt and chives)

Additives: E100-E1518, preservatives or artificial colors, gelling agents, thickening matter, humectant, emulsifiers, flavor potentiators, antioxidants, separating agents, sweeteners, baking agents, modified starches, foaming agents, stabilizers, flavoring agents

Breads with additional grains, herbs, or other such added ingredients

Packaged bread is preferable to bakery bread, because the ingredients are on the label

Alcohol

Sesame

Pasta with eggs, cake, biscuits, potato chips

Margarine and mayonnaise

Eggs

Smoked meats

Seafood

Tomatoes, artichokes, peas, mushrooms, spinach, rhubarb, olives

sweet peppers

Fruit, dried fruits, and fruit juices

Herbal tea

Any substitutions not listed as acceptable in the clinical diary's guidelines

Any substance that the patient remains unsure if it is allowed or not

Use only fresh foods; no preserved foods, except deep-frozen foods without any additives

Effects of a pseudoallergen-free diet on chronic spontaneous urticaria: a prospective trial

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chronic spontaneous urticaria; intolerance reactions to food; mast cell; pseudoallergen-free diet; quality of life; urticaria activity score.

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Abstract

Background: Chronic spontaneous urticaria is a skin disorder that is difficult to manage and can last for years. ‘Pseudoallergens’ are substances that induce hypersensitive/intolerance reactions that are similar to true allergic reactions. They include food additives, vasoactive substances such as histamine, and some natural substances in fruits, vegetables and spices. Eliminating pseudoallergens from the diet can reduce symptom severity and improve patient quality of life.

Aim: To assess the effects of a pseudoallergen-free diet on disease activity and quality of life in patient’s chronic spontaneous urticaria.

Methods: Study subjects had moderate or severe chronic spontaneous urticaria that had not responded adequately to treatment in primary care. For 3 weeks, subjects followed a pseudoallergen-free diet. They kept a clinical diary, which recorded their wheal and pruritus severity each day, to yield a clinical rating of chronic spontaneous urticaria severity (the UAS4 score). The subjects also completed the DLQI, a validated quality-of-life instrument. Use of antihistamines and glucocorticoids was minimized, recorded, and analysed. Subjects were classified into nine response categories, according to the changes in symptom severity (UAS4), quality of life (DLQI) and medication usage.

Results: From the 140 subjects, there were 20 (14%) strong responders and 19 (14%) partial responders. Additionally, there were nine (6%) subjects who made a substantial reduction in their medication without experiencing worse symptoms or quality of life.

Conclusions: Altogether the pseudoallergen-free diet is beneficial for one in three patients. The pseudoallergen-free diet is a safe, healthy and cost-free measure to identify patients with chronic spontaneous urticaria that will benefit from avoiding pseudoallergens.

Chronic spontaneous urticaria (CSU) is a common skin disorder, characterized by spontaneously arising itchy wheals and/or angioedema present on a regular basis for longer than 6 weeks (1–5). In the majority of cases, the cause remains unidentified (4, 5), so the patient attempts to suppress symptoms with antihistamines or other medications, often for many years. Although these medications can be effective, they do not eliminate the cause of CSU, they require ongoing usage (which is costly), they have side-effects and risks (e.g. sedation with first generation antihistamines, weight gain and high blood pressure/sugar levels with systemic glucocorticoids), and many patients still report insufficient symptom control (4, 5). Because of several

reports by various specialized urticaria clinics, it is now known that pseudoallergens induce and/or aggravate urticaria in many patients (6–8). These pseudoallergens include artificial preservatives and dyes in modern processed food and aromatic compounds in some natural foods. Previous studies have supported the effectiveness of a pseudoallergen-free diet in reducing CSU severity (9–12). After several months of not eating the triggering pseudoallergens, most patients can eat normally again without developing urticaria. So in contrast to medications, a pseudoallergen-free diet actually cures urticaria rather than simply suppressing symptoms, and it involves no additional cost to the patient or the healthcare system. The aim of this study was to

assess how many CSU patients benefit from a pseudoallergen-free diet and how much they actually benefit.

Methods

Subjects

Subjects were recruited from our urticaria specialist clinic, which requires referral from a dermatologist or allergist. Thus patients had to have been diagnosed with CSU and in most cases had already failed treatment at the primary care level for a while. A total of 140 CSU patients were enrolled in this study. Patient whose CSU did not seem severe or had lasted less than half a year were not included, under the assumption that their CSU will resolve spontaneously. Patients with episodic CSU (only a few episodes per year for only a few weeks) were not offered participation in the diet, under the assumption that food additives are not the cause of their CSU. Patients were also excluded if, in the opinion of the intake physician, they were unsuitable to participate, for example, due to old age, many or severe co-morbidities, inability to be compliant or complete the clinical diary, inability to stop usage of betablockers, etc. Patients under 18 were allowed to participate in the pseudoallergen-free diet program but were excluded from the research analysis. This study was conducted according to the Declaration of Helsinki and all subjects provided informed consent.

Subjects who participated in the study but who did not fill out the clinical diary correctly were excluded from the database, because it would not be possible to calculate their Urticaria Activity Score (UAS4) (explained below). Patients with a UAS4 < 9 have mild urticaria, so it would be difficult to gauge their improvement and attribute it with certainty to the diet. So although they participated fully in the study, subjects with a baseline UAS4 < 9 were excluded from this analysis.

Diet and medication regimen

Subjects kept a clinical diary for 31 days, which also provided several pages of patient education about urticaria. On days 1–7, they were instructed to eat their usual foods. On days 8–10, they were allowed only rice, potatoes, bread, butter, salt, olive oil and plain coffee or tea. On days 11–31 they followed a pseudoallergen-free diet, whereby the clinical diary listed what they were to eat at each meal. Essentially, the diet eliminates all processed foods, artificial substances, food additives, dyes, antibiotics, preservatives, phenols, and natural foods rich in aromatic compounds such as tomatoes (full details available as online supplement). Explicitly prohibited foodstuffs are listed in Box 1. After completion of the diet, the subjects were admitted as in-patients to our hospital, where they underwent further testing and assessment.

Subjects were instructed in writing that antihistamines were allowed only for 'extreme, intolerable itching' during days 1–7 and 25–31, but were allowed for 'strong itching' during days 8–24. They recorded the number of antihistamine tablets (cetirizine 10 mg, desloratadine 5 mg, ebastine 10 mg,

levocetirizine 5 mg, loratadine 10 mg or fexofenadine 180 mg) that they used each day in a clinical diary. The number of antihistamine tablets used on days 3–7 was totalled for baseline usage, and the number of tablets used on days 27–31 was totalled for final usage. The antihistamine 5 day change (AH5-change) was calculated as the baseline total minus the final total.

If necessary, subjects were administered glucocorticoids as rescue medication. The dosage was recorded in the clinical diary. The mg dosage of glucocorticoids was totalled for days 3–7 (baseline) and days 27–31 (final). The glucocorticoid 5 day change (GC5-change) was calculated as the baseline total minus the final total. (We verified that coding by mg dosage would yield more conservative results than simply coding the total number of days glucocorticoids were administered.)

Subjects were instructed to not use nonsteroidal anti-inflammatory medications. Subjects were requested to forego all other medications not absolutely necessary, including homeopathic substances, plant preparations, vitamins, minerals, etc. Any necessary medications were documented in the clinical diary.

Outcome measures

The subjects kept a clinical diary, which serves as the basis of the Urticaria Activity Score (UAS) (13). The UAS measures

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 Breads with additional grains, herbs, or other such added ingredients
 Packaged bread is preferable to bakery bread, because the ingredients are on the label
 Alcohol
 Sesame
 Pasta with eggs, cake, biscuits, potato chips
 Margarine and mayonnaise
 Eggs
 Smoked meats
 Seafood
 Tomatoes, artichokes, peas, mushrooms, spinach, rhubarb, olives
 sweet peppers
 Fruit, dried fruits, and fruit juices
 Herbal tea
 Any substitutions not listed as acceptable in the clinical diary's guidelines
 Any substance that the patient remains unsure if it is allowed or not
 Use only fresh foods; no preserved foods, except deep-frozen foods without any additives

two symptoms – quantity of wheals and intensity of itching – each on a 0–3 scale each day. The UAS4 is the sum of these two daily ratings from four consecutive days, yielding a total score of 0–24. The UAS4 was calculated for baseline (days 4–7) just before beginning the diet and for final (days 28–31) during the last days of the diet. The UAS4-change score was UAS4-baseline minus UAS4-final. The clinical diary also recorded ‘swelling’. Patients were coded positively for angioedema if they checked ‘swelling’ even once on days 4–7, negatively for angioedema if they checked ‘no swelling’ on all four days, and ‘unknown’ otherwise.

The subjects also filled out the Dermatology Quality of Life Instrument (DLQI) on days 7 (baseline) and 31 (final) of the diet. The DLQI is a well-established quality of life questionnaire, consisting of 10 questions and yielding a score of 0–30 (14–16). The DLQI-change score was DLQI-baseline minus DLQI-final.

Responder status definitions

All subjects were coded into one of nine categories, according to the criteria below. In establishing these categories, we considered that a change of four points on the UAS4 is clinically meaningful. The minimal important difference on the DLQI has been shown to be 3 points (17), and a DLQI score of <6 means that the skin condition has ‘little or no effect’ on the patient’s life (18).

‘Strong responders’ met the following criteria:

- (a) UAS4 improvement ≥ 8 (or ≥ 6 if UAS4-baseline < 13); and
- (b) DLQI-improvement ≥ 3 or DLQI-final < 6.

‘Partial responders’ met the following criteria:

- (a) subjects did not meet the criteria for ‘strong responder’;
- (b) UAS4 improvement ≥ 4 ; and
- (c) DLQI improvement ≥ 3 or DLQI-final < 6.

‘Natural-coping subjects’ met the following criteria:

- (a) subjects did not meet the criteria for ‘strong responders’ or ‘partial responder’;
- (b) UAS4 improvement ≥ 0 ;
- (c) DLQI improvement ≥ 0 or DLQI-final < 6;
- (d) AH5 reduction ≥ 3 or GC5 reduction > 0;
- (e) AH5-change not > 0; and
- (f) GC5-change not > 0.

In other words, they made a meaningful reduction of their medication without getting worse.

‘Disqualified’ subjects were subjects who met the criteria for ‘strong responder’ or ‘partial responder’ but for whom AH5 increase > 0 or GC5 increase > 0. In other words, their medication usage was higher on days 27–31 than it was on days 3–7, thus confounding the effects of the diet.

‘Nonresponders’ were all the subjects who did not meet the criteria for any of the other categories above or below.

‘Unknown’ were subjects who could not be definitively assigned to a single category due to missing data.

‘Addictive subjects’ met the following criteria:

- (a) UAS4 improvement ≥ 4 ; and
- (b) DLQI deterioration ≥ 3 .

In other words, these subjects’ physical symptoms improved but their quality of life deteriorated. Essentially the ‘cure’ was worse than the disease for these subjects; they preferred their life being able to eat their usual foodstuffs even though it exacerbates their CSU.

‘Sick-role subjects’ met the following criteria:

- (a) UAS4 deterioration ≥ 4 ; and
- (b) DLQI-improvement ≥ 3 .

In other words, these subjects’ physical symptoms deteriorated but their quality of life improved. Essentially these subjects enjoy being in the sick-role or had psychological issues that were relieved by being in treatment; their life seems better to them when they are physically sicker and following a medical regimen.

‘Deteriorated responders’ met the following criteria:

- (a) UAS4 deterioration ≥ 4 ; and
- (b) DLQI deterioration ≥ 3 .

Of course this does not mean that the pseudoallergen-free diet made their CSU worse. Some of these patients drastically reduced their antihistamine usage. Rather, patients may have deteriorated simply because of random fluctuation of CSU severity. If so, then presumably an equal number of patients who benefited improved because of random fluctuation of CSU rather than because of the diet.

Autologous serum skin test

All patients received intradermal injections of 50 μ L of histamine (positive control), sterile normal saline (negative control), autologous serum as described previously (19). Autologous serum was obtained by means of collection of venous blood into sterile glass tubes without accelerator or anticoagulant (Vacutainer; Becton Dickinson, Franklin Lakes, NJ).

Results

Subjects

The subjects’ baseline characteristics are presented in Fig. 1. Swelling (angioedema) was recorded in 95 (68%) of the subjects and was absent in 35 (25%) of the subjects. The possible trigger factors reported by the subjects are presented in Table 1.

Clinical response

As can be seen in Table 2, 48 of 140 patients (=34%) benefited from the pseudoallergen-free diet. 20 of these 48 patients were strong responders, 19 were partial responders, and 9 were ‘natural coping’ subjects. In contrast, 92 patients (=64%) did not benefit from the diet and 22 of these patients deteriorated while on the diet. Ordinal regression

analysis revealed that neither patient sex, nor age, nor angioedema status had a significant influence on their general responder category (benefited, neutral, deteriorated).

When we assessed all 140 patients for autoreactivity by performing the autologous serum skin test (ASST), we found that only 8 of 48 (=17%) patients who benefited from the pseudoallergen-free diet were ASST positive ($P < 0.0359$) as compared to 25 of 70 (=36%) patients who showed no change under the diet. Patients that benefited from the diet were also less likely to be ASST+ when compared with those who showed no change or deteriorated under the diet ($P < 0.0477$).

Discussion

The pseudoallergen-free diet is a safe and effective way to identify patients with CSU that benefit from avoiding foods containing pseudoallergens. Our findings suggest that intolerance to pseudoallergens importantly contributes to disease activity in one in three patients with moderate or severe CSU: There were 20 strong responders and 19 partial responders, and all these subjects showed symptom allevia-

tion and improvement of quality of life, without increasing their medication usage. Another nine subjects were able to substantially reduce their medication usage without having worse symptoms or quality of life. Additionally, some of the 'nonresponders' actually achieved a meaningful improvement of either physical symptoms or quality of life but not both (data not shown).

Many patients believe that 'food allergies' are the cause of their CSU. In our study, less than 10% of the patients listed food as a possible trigger of their CSU, but this was probably because the clinical diary was understood as asking for CSU triggers on that specific day during the diet. In a classic paper on CSU, it was found that 30% of patients believe food provokes attacks of urticaria (20). According to further unpublished data from a patient survey we recently presented (21, 22), 22.5% of respondents believe that allergy to food or medicine has triggered chronic hives episodes for them in the past. Whether patients are right or not about this, it is clear that many of them believe that food is causing their CSU. It is therefore sensible that physicians address the patients' hypothesis by prescribing the pseudoallergen-free diet. Even if patients do not improve clinically, they will feel that the physician has listened earnestly to their own beliefs, which should strengthen the doctor-patient relationship.

Interestingly, we found by autologous serum skin testing that autoreactivity, a major underlying cause of CSU, is sig-

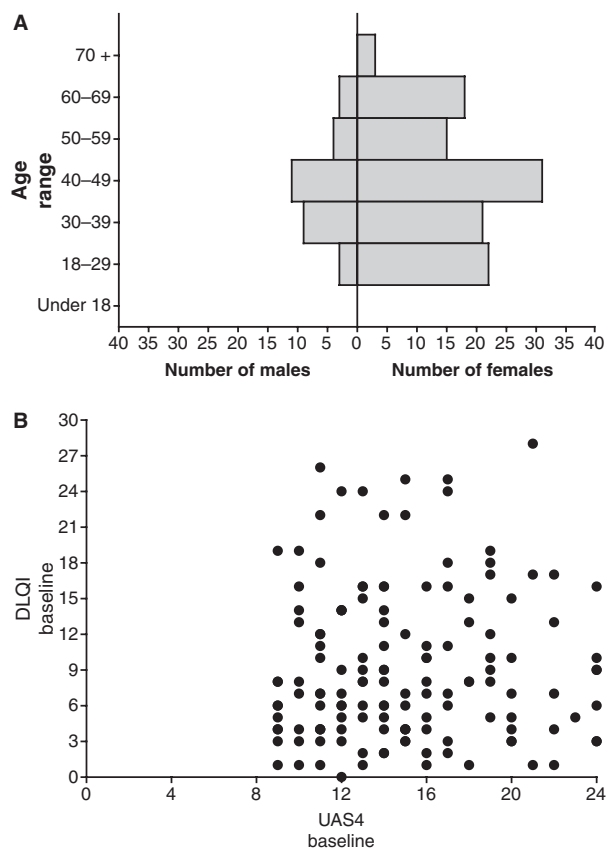


Figure 1 (A) Population pyramid, showing the study populations distribution by sex and age ranges. (B) Scatter plot of UAS4 and DLQI scores at baseline. Each dot represents one subject in the study.

Table 1 List of the subjects' replies about possible trigger factors during days 1–7

Trigger factor	<i>n</i>	%
No reply	72	50
Stress	32	22
Lack of sleep	26	18
Exercise	24	17
Food	12	8
Pressure	10	7
Heat	9	6
Cold	8	6
Infections	6	4
Medications	4	3
Alcohol	3	2
Drinks	1	1

Table 2 Response rates

General category	<i>n</i> (%)	Specific category	<i>n</i> (%)
Benefited	48 (34)	Strong responders	20 (14)
		Partial responders	19 (14)
		Natural-coping subjects	9 (6)
Neutral	70 (50)	Disqualified	4 (3)
		Nonresponders	64 (46)
		Unknown	2 (1)
		Addictive subjects	10 (7)
Deteriorated	22 (16)	Sick-role subjects	5 (3)
		Negative responders	7 (5)

nificantly less prevalent in patients that benefit from the pseudoallergen-free diet than in those that do not. This suggests that autoreactivity and benefit from avoiding pseudoallergens are not evenly distributed over all CSU patients but rather characterize distinct subpopulations. Our results also confirm that both features can be present in the same patient (23). It would be interesting to assess the relevance of autoreactivity in those CSU patients that show remission after starting a pseudoallergen-free diet and yet continue to be ASST positive after becoming free of symptoms under diet.

The pseudoallergen-free diet can promote more generally healthy eating as well. Many of the foodstuffs excluded from the diet have dubious nutritional value (e.g. soda, processed food) and/or are detrimental to dental health (candy, colas). On the other hand, the pseudoallergen-free diet temporarily eliminates most fruits and vegetables, and therefore is in some ways unnutritious and would be unhealthy if continued longer-term. But after the initial few diagnostic weeks, responders can be challenged with more specific substances and begin adding foods back into their diet that do not provoke an urticaria reaction. This general process of analysing the patient's diet in regards to urticaria provides the physician with plenty of opportunities to counsel the patient about the general importance of healthy eating. Thus the process of the pseudoallergen-free diet may lead patients to reflect upon and reform their eating habits, leading to better general and dental health.

Our study has a few limitations that should be kept in mind. First, our study does not prove that pseudoallergy is the cause of CSU in those patients that benefited from the diet. This would require a double blind placebo controlled trial. Two, not all of the response criteria used in this study have undergone a formal assessment for their minimal important difference, that is, the minimum change that represents clinically important improvement.

It is important that CSU patients stick with the pseudoallergen-free diet for at least 3 weeks. Among the subjects who were partial or strong responders at the end of 3 weeks, nearly one in three of them either did not show substantial improvement on the UAS4 by days 19–22 or even had deteriorated by then (data not shown), despite the fact that all subjects were allowed more liberal usage of antihistamines during that phase of the study. Thus, it is not possible to judge the effectiveness of the diet before a minimum trial period of 3 weeks. Some patients may even need to persist with the diet for more than 3 weeks to show clinical response. Among our nonresponders, about one in seven of them showed substantial improvement on the UAS4 only after the third week of diet (data not shown). But this informally calculated improve-

ment rate is confounded by the fact that all subjects spent the week after diet as in-patients in our hospital rather than in their usual daily routine, and were also undergoing pseudoallergen challenge testing, so the data was not gathered under comparable conditions. Furthermore, we did not analyse the subjects' medication usage data for this fourth week, so the improvement may be due to use of antihistamines or glucocorticoids. Moreover, we do not know whether this late physical improvement led to an improvement in quality of life. Although the current study cannot easily make a direct comparison of the response rates at these later in-patient time-points, our clinical experience leads us to believe that CSU patients should continue the pseudoallergen-free diet for at least 4 or even 5 weeks, in order to identify all possible responders.

The former editor of the New England Journal of Medicine recently asserted that physicians today 'practice a very drug-intensive style of medicine. Even when lifestyle changes would be more effective, physicians and their patients believe that for every ailment and discontent there is a drug' (24). The present study shows that nearly one-third of patients can significantly reduce the severity of their CSU simply by changing their diet. Although obvious, it should be emphasized that the pseudoallergen-free diet has no side-effects and no safety risks, when kept for only the several weeks necessary. Moreover, it does not cost the patient or the healthcare system any money to implement it; whereas, conventional management of CSU costs over \$2000 per year, with nearly two-thirds due to medications (25). The pseudoallergen-free diet is also beneficial for general and dental health, which may reduce a patient's future medical costs. Thus, a three-week trial of the pseudoallergen-free diet should always be one of the first diagnostic procedures any physician recommends to every new CSU patient who does not resolve spontaneously. One in three patients will benefit clinically, and the other two in three will be reassured that 'food allergies' are not the cause of their CSU. Patients and the health care system will save an enormous amount of monetary resources by taking this approach first from the outset, rather than waiting months or even years to try it.

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